Cell Research (2016) :1-2.

www.nature.com/cr

RESEARCH HIGHLIGHT

Warm feelings for TRPM2

Cell Research advance online publication 21 October 2016; doi:10.1038/cr.2016.121

Two recent studies reveal a crucial role for the cation channel TRPM2 in sensing warm temperatures, both in the thermoregulatory center of the brain and in the somatosensory system.

Temperature directly impacts the function of biological macromolecules and every (bio)chemical reaction. To ensure that the body functions at a metabolically favorable temperature, mammals and other endotherms exhibit powerful thermoregulatory processes that maintain the body core temperature (T_{core}) within a narrow temperature band [1]. In healthy humans, T_{core} is typically maintained between 36.5 and 37.5 ºC. Deviations from normothermia of only a few degrees, for instance due to disease, drug abuse or extreme environmental conditions, can have dangerous and even fatal consequences; temperatures > 40 ºC or < 32 ºC represent an acute medical urgency.

To maintain a normal T_{core}, our body is endowed with a powerful thermoregulatory system, analogous to thermostat-based systems that regulate the temperature in buildings [1]. A part of the anterior hypothalamus, the preoptic area (POA), acts as the critical thermostat. The POA not only receives input from peripheral thermosensitive neurons that report the temperature of the skin and viscera, but also contains intrinsically temperature-sensitive neurons that respond to small changes in local brain temperature. Based on the integrated local and peripheral thermal information, the POA steers thermoregulatory processes aimed at maintaining or restoring normothermia, including cutaneous vasodilatation and sweating to lose heat, or shivering and brown adipose tissue thermogenesis to produce heat. Whereas the (patho) physiology of thermoregulation has been extensively studied in the past decades, the molecular basis of the steep temperature sensitivity of POA neurons remained elusive. Now, in a recent study published in *Science*, Song *et al.* [2] provide compelling evidence that TRPM2, a member of the transient receptor potential (TRP) superfamily of cation channels, acts as a heat sensor in warm-sensitive neurons (WSNs) of the POA.

To identify WSNs, Song *et al.* [2] performed intracellular calcium measurements in isolated POA neurons, and found that about one in six neurons exhibited a robust calcium response upon warming to 45 ºC. In their search for potential heat sensors underlying the heat responses in these WSNs, Song *et al.* focused on known temperature-sensitive and calcium-permeable ion channels, mainly members of the TRP superfamily, and used various more or less selective pharmacological tools to evaluate their functional expression in POA neurons. This approach not only allowed the authors to eliminate several TRP channels that have been implicated in peripheral thermosensation, including TRPV1-3 and TRPM3 [1, 3-6], but also revealed prominent functional expression of TRPM2 in WSNs.

TRPM2 is a broadly expressed TRP channel, with the unique feature of having a Nudix-like ADP-ribose pyrophosphatase at its C-terminal cytosolic tail [7]. While it was well established that TRPM2 is directly and synergistically activated by intracellular ADP-ribose, H2O2 and increases in temperature [8], the temperature dependence of TRPM2 had not yet been thoroughly studied in the context of thermosensation or thermoregulation. Using TRPM2-deficient mice, Song *et al.* [2] were able to demonstrate that heat responses in WSNs are dependent on TRPM2. Interestingly, whereas in isolated WSNs temperatures in the range of 45 ºC were required to evoke robust responses, heat activation was shifted to significantly lower temperatures when analyzed in acute POA brain slices, where responses could be evoked by warming above ~38 ºC. This finding highlights that the temperature sensitivity of TRPM2 is not fixed, but can be modulated by the cellular environment and by various factors including (but not limited to) reactive oxygen species.

The discovery that TRPM2 marks WSNs in the POA allowed Song *et al.* [2] to pinpoint the role of these neurons in thermoregulation. In a first set of experiments, they investigated the consequences of eliminating TRPM2 on regulation of T_{core}. Under basal conditions, global TRPM2 knockout mice did not show any abnormalities in T_{core}. However, when fever was induced by microinjecting either PGE2 or the combination of the interleukins IL-1β and IL-6 into the POA, these TRPM2-deficient mice reached higher peak T_{core} temperatures.

Whereas these results clearly demonstrate that TRPM2 is required to counteract body heating during fever, they were not fully conclusive regarding the specific role of the WSNs in this process, considering the broad expression pattern of TRPM2 [7]. Therefore,

Song *et al.* [2] adopted a method using DREADDs (Designer Receptors Exclusively Activated by Designer Drugs), engineered G-protein coupled receptors that can be activated by clozapine-N-oxide (CNO) and that couple to either stimulatory (G_q-DREADD) or inhibitory (G_i-DREADD) G proteins. Song *et al.* introduced the DREADDs specifically in TRPM2-expressing WSNs by stereotactic injection of Cre-inducible viral constructs in TRPM2-Cre mice, and then monitored the effects of CNO on T_{core}. Strikingly, activation of the TRPM2-positive WSNs in the G_q-DREADD-expressing mice caused a drop in T_{core} to ~27 ºC, which lasted several hours and could be repeated multiple times. Infrared imaging of the treated mice further indicate that the striking decrease in T_{core} correlated with cutaneous vasodilation, resulting in heat loss, as well as with reduced activity of brown adipose tissue, reflecting reduced heat production. Oppositely, inhibition of the TRPM2-expressing WSNs with Gi-DREADD resulted in a significant but mild (~1 ºC) increase in T_{core}, suggesting that WSNs exhibit some degree of tonic activity. Overall, these results provide compelling evidence that TRPM2-positive WSNs steer powerful processes that result in a reduction of T_{core}.

Song *et al.* [2] also provide a first insight into how activation of WSNs in the POA is coupled to thermoregulatory physiological responses. They found that the strong drop in T_{core} is initiated by a subset of TRPM2-positive WSNs that express the vesicular glutamate transporter Vglut2 and project onto the paraventricular nucleus of the hypothalamus (PVH). In particular, the authors provide evidence that the WSNs excite PVH neurons that release corticotropin-releasing hormone (Crh). These results provide a basis for further research on the physiological relevance of Crh release in thermoregulation.

In an independent recent study in *Nature*, Tan and McNaughton [9] implicate TRPM2 in detecting non-painful warmth in the peripheral nervous system. They describe a subset of heat-activated neurons in sensory neurons from dorsal root ganglia (DRG) as well as in sympathetic neurons from the superior cervical ganglion (SCG) that do not express the known heat-activated TRPV1-4 or TRPM3 channels. Heat responses in this population of DRG and SCG neurons were potentiated by H_2O_2, and reduced in TRPM2-knockout mice [9]. At the behavioral level, TRPM2-deficient mice are unable to discriminate between 33 ºC and 38 ºC in a two-plate preference test, suggesting a specific deficit in innocuous warmth sensing.

The studies of Song *et al.* and Tan and McNaughton identify TRPM2 as a central element of mammalian thermoregulation, implicated in both central and peripheral temperature sensing in the narrow thermal range around 37 ºC. These findings reinforce the central role of TRP channels as molecular thermometers, and may open new avenues for the clinically controlled modulation of T_{core}. For instance, there is evidence that mild hypothermia can reduce neurological damage after stroke or cardiac arrest [10], therefore targeted activation of TRPM2-expressing WSNs in the POA may represent an alternative approach to current elaborate physical cooling procedures.

Thomas Voets[1]

[1]*Laboratory of Ion Channel Research and TRP Research Platform Leuven (TRPLe), Department of Cellular and Molecular Medicine, University of Leuven, Belgium*
Correspondence: Thomas Voets
E-mail: thomas.voets@kuleuven.be

References

1 Vriens J, Nilius B, Voets T. *Nat Rev Neurosci* 2014; **15**:573-589.
2 Song K, Wang H, Kamm GB, *et al. Science* 2016 Aug 25. doi:10.1126/science.aaf7537
3 Caterina MJ, Leffler A, Malmberg AB, *et al. Science* 2000; **288**:306-313.
4 Davis JB, Gray J, Gunthorpe MJ, *et al. Nature* 2000; **405**:183-187.
5 Moqrich A, Hwang SW, Earley TJ, *et al. Science* 2005; **307**:1468-1472.
6 Vriens J, Owsianik G, Hofmann T, *et al. Neuron* 2011; **70**:482-494.
7 Faouzi M, Penner R. *Handb Exp Pharmacol* 2014; **222**:403-426.
8 Togashi K, Hara Y, Tominaga T, *et al. EMBO J* 2006; **25**:1804-1815.
9 Tan CH, McNaughton PA. *Nature* 2016; **536**:460-463.
10 Dumitrascu OM, Lamb J, Lyden PD. *J Cereb Blood Flow Metab* 2016; **36**:1157-1164.